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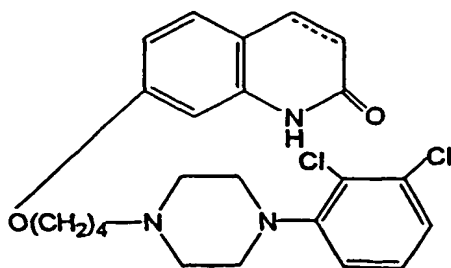
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Tokushima 771-0104 (JP). **TOTTORI, Katsura**; 15-1,*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*(54) Title: 5-HT_{1A} RECEPTOR SUBTYPE AGONIST

(1)

(57) Abstract: The present invention relates to use of
a compound for the production of a medicament for
treating a patient suffering from a disorder of the central
nervous system associated with 5-HT_{1A} receptor subtype,
which the medicament comprising as an active ingredient
a carbostyryl derivative or a salt thereof represented by
the formula (1), wherein the carbon-carbon bond between
3- and 4-positions in the carbostyryl skeleton is a single
or a double bond; and a pharmaceutically acceptable salt
or solvate thereof.

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5-HT_{1A} RECEPTOR SUBTYPE AGONIST

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype. The active ingredient comprise a carbostyryl derivative or a salt thereof.

RELATED ART

U.S. Patent No. 5,006,528; European Patent No. 367,141 and Japanese Patent Kokai (Laid-open) 7-304,740 (1995) contain the same chemical structural formula as the carbostyryl derivatives in the present invention, and their pharmacological properties are beneficial drug treatments for schizophrenia.

Carbostyryl compounds, as well as those disclosed in Japanese Patent Kokai (Laid-open) 9-301,867 (1997) are useful for the treatment of anxiety.

The carbostyryl derivatives disclosed in European Patent No. 226,441 have the genus of the carbostyryl derivatives in the present invention, and they are useful for the treatment of hypoxia.

In addition to the above, the carbostyryl derivatives disclosed in U.S. Patent No. 4,734,416; Canadian Patent No. 1,117,110; British Patent No. 2,017,701; German Patent Nos. 2,911,108, 1,912,105 and

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2,953,723; Japanese Patent Kokai (Laid-open) Nos. 54-130,587 (1979), 55-127,371 (1980) and 62-149,664 (1987) have the genus of the carbostyryl derivatives in the present invention, and they have antihistaminic
5 activities and central nervous controlling activities.

It is reported that aripiprazole (7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydro-carbostyryl, also known as, OPC-14597, BMS-337,039 and OPS-31) binds with high affinity to dopamine D₂
10 receptors and with moderate affinity to dopamine D₃ and 5-HT₁ receptors (Masashi Sasa et al., CNS Drug Reviews, Vol. 3, No. 1, pp. 24-33).

Further, it is reported that aripiprazole possesses presynaptic dopaminergic autoreceptor
15 agonistic activity, postsynaptic D₂ receptor antagonistic activity, and D₂ receptor partial agonistic activity (T. Kikuchi, K. Tottori, Y. Uwahodo, T. Hirose, T. Miwa, Y. Oshiro and S. Morita: J. Pharmacol. Exp. Ther., Vol. 274, pp. 329, (1995); T. Inoue, M.
20 Domae, K. Yamada and T. Furukawa: J. Pharmacol. Exp. Ther., Vol. 277, pp. 137, (1996)).

However, it has not been reported that compounds in the present invention have agonistic activity at 5-HT_{1A} receptor subtype.

25 It has been reported that therapeutic interventions using 5-HT_{1A} receptor ligands may be useful drug treatments for alcohol abuse (Mark Kleven et al., European Journal of Pharmacology, Vol. 281,

(1995) pp. 219-228).

It is also reported that 5-HT_{1A} agonist drugs may be useful for the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events in mammals (U.S. Patent No. 5,162,375).

It is also reported that 5-HT_{1A} receptor hypersensitivity could be the biological basis for the increased frequency of migraine attack in stressful and anxious conditions (Massimo Leone et al., Neuro Report, Vol. 9, pp. 2605-2608 (1998)).

It has recently been reported that (-)-(R)-2-[4-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]butyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide monohydrochloride (BAY-3702), a 5-HT_{1A} receptor agonist, has neuroprotective, anxiolytic- and antidepressant-like effects in animal models (Jean De Vry et al., European Journal of Pharmacology, Vol. 357, (1998), pp. 1-8).

It is also reported that 5-HT_{1A} receptor agonists appear to be broad spectrum antiemetic agents (Mary C. Wolff et al., European Journal of Pharmacology, Vol. 340, (1997), pp. 217-220; AB Alfieri et al., British Journal of Cancer, (1995), Vol. 72, pp. 1013-1015; Mary C. Wolff et al., Pharmacology Biochemistry and Behavior, 1995, Vol. 52, No. 3, pp. 571-575; James B. Lucot, European Journal of Pharmacology, 1997, Vol. 253, pp. 53-60).

Serotonin plays a role in several neurological and psychiatric disorders, including Alzheimer's disease, depression, nausea and vomiting, eating disorders, and migraine. (See Rasmussen et al.,
5 "Chapter 1. Recent Progress in Serotonin 5HT_{1A} Receptor Modulators", in Annual Reports in Medicinal Chemistry, Vol. 30, Section I, pp. 1-9, 1995, Academic Press, Inc.). WO 00/16777 discloses that a 5HT_{1A} receptor agonist, buspirone is efficacious in treating a variety
10 of symptoms associated with ADHD, and that combined use of a D2 receptor agonist and 5-HT_{1A} agonist provides effective treatments for ADHD and Parkinson's disease.

5HT_{1A} agonists are effective in the treatment of cognitive impairment in Alzheimer's disease,
15 Parkinson's disease or senile dementia. US 5824680 discloses that a 5-HT_{1A} agonist, ipsapirone, is effective in treating Alzheimer's disease by improving memory. US 4687772 describes that a 5-HT_{1A} partial agonist, buspirone, is useful for improving short term
20 memory in patients in need of treatment. WO 93/04681 discloses that use of 5-HT_{1A} partial agonists have been used for the treatment or prevention of cognitive disorders associated with Alzheimer's disease, Parkinson's disease or senile dementia.

25 5HT_{1A} agonists are also effective in the treatment of depression. US 4771053 describes that a 5-HT_{1A} receptor partial agonist, gepirone, is useful in alleviation of certain primary depressive disorders,

such as severe depression, endogenous depression, major depression with melancholia, and atypical depression. WO 01/52855 discloses that the combined use of the 5-HT_{1A} receptor partial agonist gepirone with an
5 antidepressant can effectively treat depression.

The 5-HT_{1A} receptor partial agonist buspirone alleviates motor disorders such as neuroleptic induced parkinsonism and extrapyramidal symptoms. These observations are disclosed in US 4438119. Furthermore
10 5-HT_{1A} agonists reverse neuroleptic-induced catalepsy in rodents, which mimic movement impairments observed in Parkinson's disease (Mark J. Millan, Journal of Pharmacology and Experimental Therapeutics, 2000, Vol. 295, p853-861). Thus, aripiprazole can be used to
15 manage psychosis in geriatric patients, Alzheimer's disease, Parkinson's disease or senile dementia, since it possesses potent, partial agonistic activities at D₂ and 5-HT_{1A} receptors. In addition, these patients might not experience extrapyramidal symptoms due to this
20 property of aripiprazole.

Heretofore, schizophrenia is understood to be caused by hyperactivity in the brain dopaminergic system. For this reason, some drugs were developed with strong dopaminergic receptor blocking activity.
25 These typical antipsychotic drugs are effective in the treatments for the positive symptoms of schizophrenia, which include hallucinations, delusions and the like. During the last decade, a variety of atypical anti-

psychotic drugs have been developed, which include
clozapine, risperidone, olanzapine, quetiapine. These
drugs have less extrapyramidal side effects, and have
other activities in addition to their DA-receptor
5 blocking activities. In contrast to typical anti-
psychotic drugs, such as chlorpromazine, haloperidol,
etc., it is reported that atypical antipsychotic drugs
are more effective against the negative symptoms and
cognitive impairments associated with schizophrenia
10 than typical antipsychotic drugs, and atypical
antipsychotic drugs also have less extrapyramidal side
effects (S. Miyamoto, G. E. Duncan, R. B. Mailman and
J. A. Lieberman: Current Opinion in CPNS Investiga-
tional Drugs, Vol. 2, pp. 25, (2000)). However, even
15 though atypical antipsychotic drugs provide a suitable
pharmacotherapy for schizophrenia, certain patients are
resistant to the antipsychotic therapies of these
drugs. These patients may either not respond or may
become refractory (i.e. may feel more anxious,
20 depressed or cognitive dysfunction) in response to
antipsychotic therapy. These treatment-resistant
patients pose a problem for how a physician may provide
an appropriate therapy.

At present, a number of treatment-resistant
25 and treatment-refractory schizophrenic patients display
symptoms that do not respond adequately to a variety of
known effective classes and doses of typical or
atypical antipsychotic drugs. Furthermore, these

patients may also be inveterate schizophrenia or chronic schizophrenics who are often repeatedly admitted to and discharged from hospitals (R. R. Conely and R. W. Buchanan: Schizophr. Bull., Vol. 23, pp. 663, 5 (1997)).

Symptoms of patients corresponding to treatment-resistant and treatment-refractory schizophrenics involve not only the positive symptoms, but also the negative symptoms and emotional disorders, 10 as well as cognitive impairments (i.e., cognitive dysfunction or cognitive disturbances) (K. Akiyama and S. Watanabe: Jpn. J. Clin. Psychopharmacol., Vol. 3, pp. 423, (2000)).

Cognitive impairment exists separately from 15 the psychic symptoms in a schizophrenic individual. Thus, medical treatment is therefore quite important, because the cognitive impairment may disturb the socially adaptable behavior of these individuals (C. Hagger, P. Buckley, J. T. Kenny, L. Friedman, D. Ubogy 20 and H. Y. Meltzer: Biol. Psychiatry, Vol. 34, pp. 702, (1993); T. Sharma and D. Mockler: J. Clin. Psychopharmacol., Vol. 18, (Suppl. 1), pp. 128, (1998)).

At present, clozapine is an antipsychotic drug that is effective against treatment-resistant 25 schizophrenia. Clozapine (marketed under the name of Clozaril) was approved in 1990 by FDA for the treatment and management of severely ill schizophrenics who failed to respond adequately to standard antipsychotic

therapy (M. W. Jann: Pharmacotherapy, Vol. 11, pp. 179, (1991)). Clozapine has been reported to be effective against cognitive impairments in treatment-resistant schizophrenics (C. Hagger, P. Buckley, J. T. Kenny, L. Friedman, D. Ubogy and H. Y. Meltzer: Biol. Psychiatry, Vol. 34, pp. 702, (1993); M. A. Lee, P. A. Thompson and H. Y. Meltzer: J. Clin. Psychiatry, Vol. 55 (Suppl. B), pp. 82, (1994); D. E. M. Fujii, I. Ahmed, M. Jokumsen and J. M. Compton: J. Neuropsychiatry Clin. Neurosci., Vol. 9, pp. 240, (1997)). For example, it is reported that clozapine improves cognitive impairments in attention, response time, fluent-speech, etc. in treatment-resistant schizophrenics (M. A. Lee, P. A. Thompson and H. Y. Meltzer: J. Clin. Psychiatry, Vol. 55 (Suppl. B), pp. 82, (1994)). It has been also reported that clozapine provides effective improvements in cognitive impairments in an objective evaluation scale of the Wechsler Adult Intelligence Scale-Revised Full Scale (D. E. M. Fujii, I. Ahmed, M. Jokumsen and J. M. Compton: J. Neuropsychiatry Clin. Neurosci., Vol. 9, pp. 240, (1997)).

The 5-HT_{1A} receptor has been demonstrated to play a role in the therapeutic efficacy of clozapine against treatment-resistant schizophrenia and cognitive impairments. This relationship was revealed by a binding experiment using human 5-HT_{1A} receptors (S. L. Mason and G. P. Reynolds: Eur. J. Pharmacol., Vol. 221, pp. 397, (1992)). Further, in accordance with

progress in molecular pharmacology, it is clearly understood that 5-HT_{1A} receptor agonistic activity or 5-HT_{1A} receptor partial agonistic activity plays an important role in treatment-resistant schizophrenia and cognitive impairments (A. Newman-Tancredi, C. Chaput, L. Verrielle and M. J. Millan: Neuropharmacology, Vol. 35, pp. 119, (1996)). Additionally, it was reported that the number of 5-HT_{1A} receptor is increased in the prefrontal cortex of chronic schizophrenics who were classified treatment-resistant. This observation was explained by a compensatory process where by the manifestation of severe symptoms of chronic schizophrenia are a result of impaired neuronal function mediated by hypofunctional 5-HT_{1A} receptors (T. Hashimoto, N. Kitamura, Y. Kajimoto, Y. Shirai, O. Shirakawa, T. Mita, N. Nishino and C. Tanaka: Psychopharmacology, Vol. 112, pp. S35, (1993)). Therefore, a lowering in neuronal transmission mediated through 5-HT_{1A} receptors is expected in treatment-resistant schizophrenics. Thus the clinical efficacy of clozapine may be related to its partial agonist efficacy at the 5-HT_{1A} receptors (A. Newman-Tancredi, C. Chaput, L. Verrielle and M. J. Millan: Neuropharmacology, Vol. 35, pp. 119, (1996)). 5-HT_{1A} receptor agonistic activity may be related to the clinical effects of clozapine, and this hypothesis is supported by a positron emission tomography study in primates which showed that clozapine interacts with brain 5-HT_{1A}

receptors at a therapeutically effective dose (Y. H. Chou, C. Halldin and L. Farde: Int. J. Neuropsychopharmacol., Vol. 4 (Suppl. 3), pp. S130, (2000)).

Furthermore tandospirone, which is known as a selective
5 5-HT_{1A} receptor agonist, improved cognitive impairments
in chronic schizophrenic patients (T. Sumiyoshi, M. Matsui, I. Yamashita, S. Nohara, T. Uehara, M. Kurachi and H. Y. Meltzer: J. Clin. Pharmacol., Vol. 20, pp. 386, (2000)). While, in animal tests, all reports do
10 not always suggest that 5-HT_{1A} receptor agonist activity
may be related to cognitive impairment, however, 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin), which is known as a selective 5-HT_{1A} receptor agonist, improves
learning and memory impairments induced by scopolamine
15 known as a muscarinic receptor antagonist, suggesting a
relationship between 5-HT_{1A} receptor agonistic activity
and improvements in cognitive impairments (M. Carli, P. Bonalumi, R. Samanin: Eur. J. Neurosci., Vol. 10, pp. 221, (1998); A. Meneses and E. Hong: Neurobiol. Learn.
20 Mem., Vol. 71, pp. 207, (1999)).

Atypical antipsychotic drugs, such as risperidone and olanzapine, were marketed after clozapine, and it is reported that these drugs improve
treatment-resistant schizophrenia or cognitive impair-
25 ments in treatment-resistant schizophrenics (M. F. Green, B. D. Marshall, Jr., W. C. Wirshing, D. Ames, S. R. Marder, S. McGurck, R. S. Kern and J. Mintz: Am. J. Psychiatry, Vol. 154, pp. 799, (1997); G. Bondolfi, H.

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Dufour, M. Patris, J. P. May, U. Billeter, C. B. Eap
and P. Baumann, on behalf of the risperidone Study
Group: Am. J. Psychiatry, Vol. 155, pp. 499, (1998); A.
Breier, S. H. Hamilton: Biol. Psychiatry, Vol. 45, pp.
5 403, (1999)).

In contrast to reports that clozapine was
moderately effective against treatment-resistant
schizophrenia, risperidone and olanzapine were not
consistently superior to typical antipsychotic drugs in
10 their effectiveness against treatment-resistant
schizophrenia. Thus, risperidone and olanzapine bind
with lower affinity to human 5-HT_{1A} receptors (S.
Miyamoto, G. E. Duncan, R. B. Mailman and J. A.
Lieberman: Current Opinion in CPNS Investigational
15 Drugs, Vol. 2, pp. 25, (2000)), and as such these drugs
can not clearly perform activities through human 5-HT_{1A}
receptors at clinical effective doses.

Therefore, at present, it is understood that
clozapine is effective against treatment-resistant
20 schizophrenia (D. W. Bradford, M. H. Chakos, B. B.
Sheitman, J. A. Lieberman: Psychiatry Annals, Vol. 28,
pp. 618, (1998); A. Inagaki: Jpn. J. Clin. Psycho-
pharmacol., Vol. 3, pp. 787, (2000)).

As explained above, 5-HT_{1A} receptor agonistic
25 activity is important for improving treatment-resistant
schizophrenia or cognitive impairment caused by
treatment-resistant schizophrenia. Clozapine is
effective against treatment-resistant schizophrenia,

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however, its use is limited due to its severe side-effect of producing agranulocytosis which requires patients to undergo periodical blood tests. Under these circumstances, the development of a safe anti-
5 psychotic drug with potent, full or partial agonist activity at 5-HT_{1A} receptors is earnestly desired.

The carbostyryl compound in the present invention binds with high affinity and displays a potent, partial agonist activity at the 5-HT_{1A} receptors
10 and it has higher intrinsic activity (about 68%) as compared with that of clozapine. Therefore, the compound in the present invention has a 5-HT_{1A} receptor agonistic activity that is more potent than the agonistic activity of clozapine. Thus, the present
15 carbostyryl compound may represent a more potent and highly safe drug for curing treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by
20 inveterate schizophrenia, chronic schizophrenia, cognitive impairments caused by chronic schizophrenia and the like, as compared with other currently available pharmacotherapeutic treatments. That is, the compound in the present invention may prove to be a
25 potent and safer drug therapy for treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by inveterate

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schizophrenia, chronic schizophrenia, or cognitive impairments caused by chronic schizophrenia, etc., which fail to respond adequately to currently available antipsychotic drugs such as chlorpromazine,

5 haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozide, zotepine, risperidone, olanzapine, quetiapine, amisulpride, etc.

In particular, the carbostyryl compound in the present invention may be a potent and highly safe

10 drug therapy against treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by inveterate schizophrenia, chronic schizophrenia or cognitive impairments caused by

15 chronic schizophrenia, etc. which fail to respond adequately to both of 1 to 3 typical antipsychotic drugs selected from the group consisting of chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from the group

20 consisting of risperidone, olanzapine, quetiapine and amisulpride.

Moreover, the compound in the present invention may be a potent and highly safe drug therapy against treatment-resistant schizophrenia, cognitive

25 impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairment caused by inveterate schizophrenia, chronic schizophrenia or cognitive impairment caused by chronic

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schizophrenia, etc. which fail to respond adequately to both of 2 typical antipsychotic drugs selected from the group consisting of chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug
5 selected from the group consisting of risperidone, olanzapine, quetiapine and amisulpride.

Moreover, the compound in the present invention may be a potent and highly safe drug therapy against treatment-resistant schizophrenia, cognitive
10 impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by inveterate schizophrenia, chronic schizophrenia, cognitive impairments caused by chronic schizophrenia, etc. which fail to respond adequately to
15 both of 1 to 2 typical antipsychotic drugs selected from the group consisting of chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from the group consisting of risperidone, olanzapine, quetiapine and amisulpride.

20 Moreover, the compound in the present invention may be a potent and highly safe drug therapy against treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairment
25 caused by inveterate schizophrenia, chronic schizophrenia or cognitive impairment caused by chronic schizophrenia, etc. which fail to respond adequately to both of 2 typical antipsychotic drugs selected from the

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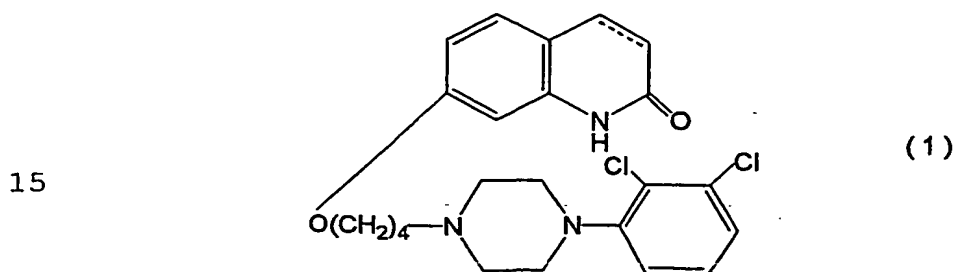
group consisting of chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from the group consisting of risperidone, olanzapine, quetiapine and amisulpride.

5 SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype.

10 DETAILED DESCRIPTION OF THE INVENTION

As the 5-HT_{1A} receptor subtype agonist compound for use in accordance with the present invention, carbostyryl derivatives represented by the following formula (1) are used:



wherein the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single or a double bond.

The compounds of the forgoing general formula
20 (1) are known compounds, which are disclosed in publication such as U.S. Pat. No. 5,006,528 or which

can be readily prepared by the processes described in the above publication.

The carbostyryl derivative represented by the formula (1) in the present invention can easily be converted into its acid-addition salt by reacting it with a pharmaceutically acceptable acid. Examples of such acid include inorganic acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; organic acids, such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid and the like.

The solvent of solvates is a solvent conventionally used in recrystallization. Examples of solvates include hemihydrates, hydrates, and alcohates, such as ethanlates, methanlates, isopropanolates and the like.

The desired compounds, prepared by the reactions mentioned above, can easily be isolated and purified by usual separation procedures such as solvent extraction, dilution, recrystallization, column chromatography, preparative thin layer chromatography and the like.

The potent, partial 5-HT_{1A} receptor agonist in the present invention is useful for various disorders of the central nervous system associated with the 5-HT_{1A} receptor subtype that induces bipolar disorders, such as bipolar I disorder with most recent hypomanic, manic, mixed, depressed or unspecified episode; bipolar

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II disorder with recurrent major depressive episodes with hypomanic episodes, and cyclothymic disorder; depression, such as endogenous depression, major depression, melancholia, and treatment-resistant depression; panic disorder; obsessive compulsive disorder (OCD); sleep disorders; sexual dysfunction; alcohol abuse and drug addiction; cognitive impairment; neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and the like, cognitive impairments caused by neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and related disorders; emesis; motion sickness; obesity; migraine; autism; Down's syndrome; attention-deficit hyperactivity disorder (ADHD); treatment-resistant, inveterate or chronic schizophrenia, (which fail to respond adequately to currently available antipsychotic drugs); cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia or chronic schizophrenia and the like.

Compounds of the present invention may be suitably prepared into pharmaceutically acceptable formulations (see U.S. Patent No. 5,006,528, European Patent No. 367,141 and Japanese Kokai (Laid-open) 7-304,740 (1995), and Japanese Patent Application No. 2000-194976 incorporated by reference herein).

The dosage of these pharmaceutical preparations of the invention may be selected appropriately depending on the method of administration, the

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patient's age, sex and other factors, severity of the disease and other factors. Generally, however, the daily dose of the active ingredient compound is preferably within the range of about 0.0001 to about 50 mg per kilogram of body weight. It is desirable that the active ingredient compound be contained in each unit dosage form in an amount of about 0.001 to about 1,000 mg, particularly 0.01 to 100 mg, more particularly, 0.1 to 50 mg, yet more particularly 1 mg to 20 mg.

Pharmacological tests

1. MATERIALS AND METHODS

1.1 Test Compound

7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl (aripiprazole) was used as test compound.

1.2 Reference Compounds

Serotonin (5-HT) and WAY-100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridimyl)-cyclohexanecarboxamide, a 5-HT_{1A} receptor antagonist, manufactured by RBI (Natick, MA) were used as reference compounds.

1.3 Vehicle

Dimethyl sulfoxide (DMSO) manufactured by Sigma Chemical Co. (St. Louis, MO) was used as vehicle.

1.4 Preparation of Test and Reference Compounds

Test compound was dissolved in 100% dimethyl

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sulfoxide (DMSO) to yield 100 μ M stock solutions (final concentration of DMSO in all tubes containing test compound was 1%, v/v). All other reference compounds were prepared by the same method using double-distilled water rather than DMSO.

1.5 Experimental Procedure for the [35 S]GTP $_{\gamma}$ S Binding Assay

Test and reference compounds were studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 5, 10, 50, 100, 1000, 10000 and 50000 nM) for their effects upon basal [35 S]GTP $_{\gamma}$ S binding to h5-HT $_{1A}$ CHO cell membranes. Reactions were performed in 5 ml glass test tubes containing 8 μ l of test/reference drug mixed with 792 μ l of buffer (25 mM Tris HCl, 50 mM NaCl, 5 mM MgCl $_2$, 0.1 mM EGTA, pH = 7.4) containing GDP (1 μ M), [35 S]GTP $_{\gamma}$ S (0.1 nM) and h5-HT $_{1A}$ CHO cell membranes (10 μ g protein/reaction; NEN Life Science Products, Boston, MA; catalog # CRM035, lot # 501-60024, GenBank # X13556). Reactions proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper, using a Brandel harvester and 4x3 ml ice-cold buffer washes. 35 S radioactivity bound to the filter paper was measured using liquid scintillation counting (1272 Clinigamma, LKB/Wallach).

1.6 Experimental Procedure to Determine the Binding Affinity of Test compound (aripiprazole) at the h5-HT $_{1A}$ Receptor

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Test compound was studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 10, 50, 100, 500, 1000, 5000 and 10000 nM) to determine its displacement of [³H]8-OH-DPAT (1 nM; NEN Life Sciences; catalog # NET 929, lot # 3406035, Specific Activity = 124.9 Ci/mmol) binding to h5-HT_{1A} receptors in CHO cell membranes (15 - 20 µg protein; NEN Life Science Products, catalog # CRM035, lot # 501-60024). Membranes (396 µl) were incubated in 5 ml glass tubes containing [³H]8-OH-DPAT (396 µl), test compound or vehicle (8 µl) and buffer A (50 mM Tris.HCl, 10 mM MgSO₄, 0.5 mM EDTA, 0.1% (w/v) ascorbic acid, pH = 7.4). All assays proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper (presoaked in buffer B; 50 mM Tris.HCl, pH = 7.4), using a Brandel harvester and 4x1 ml ice-cold washes with buffer B. Non-specific binding was determined in the presence of 10 µM (+)8-OH-DPAT.

1.7 Parameters Determined

Serotonin (5-HT) is a full 5-HT_{1A} receptor agonist which stimulates increases in basal [³⁵S]GTP_γS binding to h5-HT_{1A} receptors in recombinant CHO cell membranes. Test compound was studied at 10 concentrations to determine their effects upon basal [³⁵S]GTP_γS binding relative to that produced by 10 µM 5-HT. The relative potency (EC₅₀, 95% confidence interval) and intrinsic agonist activity (% of E_{max} for 10 µM 5-HT) was calculated for each compound by computerized non-linear

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regression analysis of complete concentration-effect data. The binding affinity of test compound at the h5-HT_{1A} receptor was determined by its ability to prevent [3H]8-OH-DPAT binding to CHO cell membranes that express this receptor. Non-linear regression analysis of the competition binding data was used to calculate an inhibition constant (IC₅₀, 95% confidence interval), which is the concentration of test compound that occupies half of the h5-HT_{1A} sites specifically bound by [3H]8-OH-DPAT. The affinity of h5-HT_{1A} receptors for test compound (K_i, 95% confidence interval) was calculated by the equation, $K_i = (IC_{50}) / (1 + ([^3H]8-OH-DPAT) / K_d)$, where the K_d for [3H]8-OH-DPAT at h5-HT_{1A} = 0.69 nM (NEN Life Sciences). All estimates of drug binding affinity, potency and intrinsic efficacy at the h5-HT_{1A} receptor were calculated using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, CA).

2. RESULTS

Test compound and 5-HT produced concentration-dependent increases above basal [³⁵S]GTP_γS binding. 1% DMSO tested alone had no effect upon basal or drug-induced [³⁵S]GTP_γS binding.

Test compound (EC₅₀ = 2.12 nM), 5-HT (EC₅₀ = 3.67 nM), potently stimulated basal [³⁵S]GTP_γS binding. Potency and intrinsic agonist efficacy estimates were derived by non-linear regression analysis with correla-

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tion coefficients (r^2) > 0.98 in each case (Table 1).

Test compound exerted partial agonist efficacies in the 65 - 70% range. WAY-100635 produced no significant change (unpaired Student's t-test) in basal [35 S]GTP $_{\gamma}$ S binding at all concentrations tested (Table 1). WAY-100635 did, however, completely inhibit the effects of 5-HT and test compound upon [35 S]GTP $_{\gamma}$ S binding to h5-HT $_{1A}$ receptors in CHO cell membranes (Table 2). Tables 1 and 2 are shown below.

10 Test compound demonstrated high affinity binding to h5-HT $_{1A}$ receptors in CHO cell membranes (IC_{50} = 4.03 nM, 95% confidence interval = 2.67 to 6.08 nM; K_i = 1.65 nM, 95% confidence interval = 1.09 to 2.48 nM).

Table 1 Potency (EC_{50}) and Intrinsic Agonist Efficacy (E_{max}) of Test compound and Reference Drugs in a h5-HT $_{1A}$ [35 S]GTP $_{\gamma}$ S CHO-cell Membrane Binding Assay.

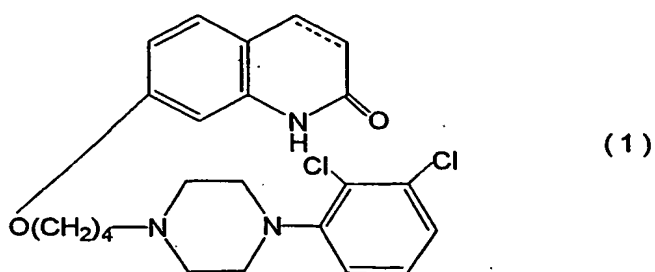
Drug	EC_{50} , nM (95% Confidence Interval)	E_{max} (% \pm SEM)	Goodness of Fit (r^2)
Test Compound	2.12 (0.87 to 5.16)	68.13 \pm 3.16	0.986
5-HT	3.67 (1.56 to 8.63)	98.35 \pm 4.47	0.986
WAY-100635	-	-	-

Table 2 Inhibitory Potency (IC_{50}) of WAY-100635 versus 1 μ M Concentration of 5-HT and Test compound in a h5-HT_{1A} [³⁵S]GTP _{γ} S CHO-cell Membrane Binding Assay.

Drug Combination	WAY-100635 Inhibition Potency, IC_{50} , nM (95% Confidence Interval)	Goodness of Fit (r^2)
5-HT + WAY-100635	217.1 (127.4 to 369.7)	0.988
Test compound + WAY-100635	392.2 (224.1 to 686.2)	0.989

CLAIMS

1. Use of a compound for the production of a medicament for treating a patient suffering from a disorder of the central nervous system associated with 5-HT_{1A} receptor subtype, which the medicament comprises a therapeutically effective amount of a carbostyryl compound of formula (1):



wherein the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

2. The use of Claim 1 wherein the disorder is depression.

3. The use of Claim 1 wherein the disorder is treatment-resistant schizophrenia, treatment-resistant schizophrenia with cognitive impairments, inveterate schizophrenia, inveterate schizophrenia with cognitive impairments, chronic schizophrenia, or chronic schizophrenia with cognitive impairments.

4. The use of Claim 3 wherein the disorder is treatment-resistant schizophrenia, inveterate schizophrenia or chronic schizophrenia, which fails to

respond adequately to currently available antipsychotic drugs.

5. The use of Claim 3 wherein the disorder is treatment-resistant schizophrenia with cognitive impairments, inveterate schizophrenia with cognitive impairments or chronic schizophrenia with cognitive impairments, which fails to respond adequately to currently available antipsychotic drugs.

6. The use of Claim 4 wherein the currently available antipsychotic drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozide, zotepine, risperidone, olanzapine, quetiapine, or amisulpride.

7. The use of Claim 5 wherein the currently available antipsychotic drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozide, zotepine, risperidone, olanzapine, quetiapine, or amisulpride.

8. The use of Claim 4 wherein the currently available antipsychotic drugs are 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

9. The use of Claim 5 wherein the currently available antipsychotic drugs are 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical

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antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

10. The use of Claim 4 wherein the currently available antipsychotic drugs are two typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

11. The use of Claim 5 wherein the currently available antipsychotic drugs are two typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

12. The use of Claim 4 wherein the currently available antipsychotic drugs are one to two typical antipsychotic drugs selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

13. The use of Claim 5 wherein the currently available antipsychotic drugs are one to two typical antipsychotic drugs selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

14. The use of Claim 4 wherein the currently available antipsychotic drugs are two typical

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antipsychotic drug selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

15. The use of Claim 5 wherein the currently available antipsychotic drugs are two typical antipsychotic drug selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

16. The use of Claim 1 wherein the disorder is autism, Down's syndrome, or attention deficit hyperactivity disorder (ADHD).

17. The use of Claim 1 wherein the disorder is a neurodegenerative disease.

18. The use of Claim 17 wherein the neurodegenerative disease is Alzheimer's disease or Parkinson's disease.

19. The use of Claim 1 wherein the disorder is panic, obsessive compulsive disorder (OCD), sleep disorders, sexual dysfunction, alcohol and drug addiction, emesis, motion sickness, obesity or migraine.

20. The use of Claim 1-19 wherein the carbostyryl compound is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyryl.

21. The use of claim 1 wherein the disorder is depression, such as endogenous depression, major

depression, melancholia or treatment-resistant depression; sexual dysfunction; alcohol abuse and drug addiction; cognitive impairments; neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease; autism; attention deficit hyperactivity disorder (ADHD); cognitive impairment caused by treatment-resistant schizophrenia, cognitive impairment caused by inveterate schizophrenia, or cognitive impairment caused by chronic schizophrenia.

22. The use of claim 1 wherein the disorder is depression, such as endogenous depression, major depression, melancholia or treatment-resistant depression.

23. The use of claim 1 wherein the disorder is cognitive impairment caused by treatment-resistant schizophrenia, cognitive impairment caused by inveterate schizophrenia, cognitive impairment caused by chronic schizophrenia.

24. The use of claim 23 wherein the disorder is cognitive impairment caused by treatment-resistant schizophrenia, cognitive impairment caused by inveterate schizophrenia, cognitive impairment caused by chronic schizophrenia, which fails to respond adequately to currently available antipsychotic drugs.

25. The use of claim 24 wherein the currently available antipsychotic drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozone, zotepine, risperidone,

olanzapine, quetiapine, or amisulpride.

26. The use of claim 24 wherein the currently available antipsychotic drugs are 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

27. The use of claim 24 wherein the currently available antipsychotic drugs are two typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

28. The use of claim 24 wherein the currently available antipsychotic drugs are one to two typical antipsychotic drugs selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

29. The use of claim 24 wherein the currently available antipsychotic drugs are two typical antipsychotic drug selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

30. The use of claim 1 wherein the disorder is cognitive impairment caused by neurodegenerative disease.

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31. The use of claim 30 wherein the cognitive impairment caused by neurodegenerative disease is Alzheimer's disease or Parkinson's disease.

32. The use of claims 21-31 wherein the carbostyryl compound is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyryl.

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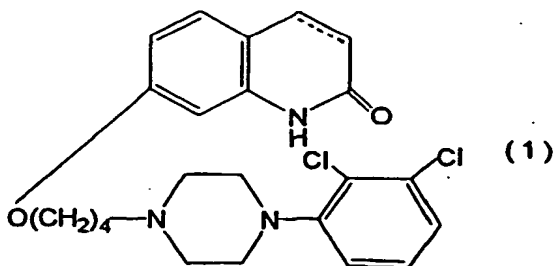
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED CARBOSTYRIL DERIVATIVES AS 5-HT_{1A} RECEPTOR SUBTYPE AGONISTS



(57) Abstract: The present invention relates to use of a compound for the production of a medicament for treating a patient suffering from a disorder of the central nervous system associated with 5-HT_{1A} receptor subtype, which the medicament comprising as an active ingredient a carbostyryl derivative or a salt thereof represented by the formula (1), wherein the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/496 A61K45/06 A61P25/24 A61P25/18
 A61P25/28 A61P25/16 A61P25/06 A61P25/30 A61P15/00
 A61P3/04 A61P1/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LIEBERMAN JEFFREY A: "Atypical antipsychotic drugs as a first-line treatment of schizophrenia: A rationale and hypothesis." JOURNAL OF CLINICAL PSYCHIATRY, vol. 57, no. SUPPL. 11, 1996, pages 68-71, XP008005973 ISSN: 0160-6689 abstract tables 2,3 page 69, column 2, paragraph 1 - paragraph 2 page 70, column 1, paragraph 2 --- -/---</p>	1,3-15, 20,21, 23-29,32

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

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21/11/2002

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Cielen, E

INTERNATIONAL SEARCH REPORT

In International Application No

PCT/JP 02/00626

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 4 764 416 A (OGURA AKEMI ET AL) 16 August 1988 (1988-08-16) cited in the application abstract column 1, line 5 - line 60 column 2, line 49 - column 3, line 22 column 6, line 41 - line 42 column 29, line 15 - line 24 column 33, line 1 examples 54, 205, 233, 258, 294 claims 21, 28</p> <p>----</p>	<p>1, 2, 19-22, 32</p>
X	<p>DATABASE WPI Week 199806 Derwent Publications Ltd., London, GB; AN 1998-059088 XP002209299 JIYOUTEI YASUFUMI; NAKAI SHOZO ET AL.: "Antianxiety agent" & JP 09 301867 A (OTSUKA PHARMA CO LTD), 25 November 1997 (1997-11-25) cited in the application abstract</p> <p>----</p>	<p>1, 19, 20</p>
X	<p>EP 0 367 141 A (OTSUKA PHARMA CO LTD) 9 May 1990 (1990-05-09) cited in the application abstract page 3, line 4 - line 7 page 3, line 29 - line 36 example 1 claims 12, 13, 22, 23, 26-28, 31-33</p> <p>----</p>	<p>1, 20</p>
Y	<p>WO 98 08817 A (AMERICAN HOME PROD) 5 March 1998 (1998-03-05)</p> <p>abstract page 6, line 6 - line 7 page 7, line 9 - line 14 page 20, line 1 - line 9</p> <p>----</p> <p>-/--</p>	<p>1-3, 17-22, 30-32</p>

INTERNATIONAL SEARCH REPORT

In International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PRINSSSEN ERIC P M ET AL: "Interactions between neuroleptics and 5-HT_{1A} ligands in preclinical behavioral models for antipsychotic and extrapyramidal effects." PSYCHOPHARMACOLOGY, vol. 144, no. 1, May 1999 (1999-05), pages 20-29, XP002209298 ISSN: 0033-3158 abstract page 20, column 2, paragraph 1 -page 21, column 1, paragraph 2 page 25, column 2, paragraph 2 -page 26, column 1, paragraph 1 page 26, column 1, paragraph 3 -column 2, paragraph 2 page 27, column 1, paragraph 2 - paragraph 3 page 27, column 2, paragraph 3</p>	1,3-13, 20
Y	<p>WO 94 09765 A (UNIV NEW YORK) 11 May 1994 (1994-05-11) abstract page 5, line 7 - line 37 page 6, line 25 -page 7, line 3 page 11, line 18 -page 12, line 2 page 28, line 18 - line 22 page 30, line 32 -page 31, line 18 claims 1,14,16</p>	1,2, 16-22, 30-32
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Y	<p>WO 99 38864 A (AMERICAN HOME PROD) 5 August 1999 (1999-08-05) abstract page 1, line 6 - line 11 page 6, line 1 page 6, line 16 - line 24</p>	1,2, 17-20, 30-32
A	<p>UWAHODO YASUFUMI ET AL: "Pharmacological profile of OPC-14597, a novel antipsychotic drug (2): Weak extrapyramidal side effects." JAPANESE JOURNAL OF PHARMACOLOGY, vol. 67, no. SUPPL. 1, 1995, page 144P XP008005977 68th Annual Meeting of the Japanese Pharmacological Society;Nagoya, Japan; March 25-28, 1995 ISSN: 0021-5198 the whole document</p>	1,3-15, 20-29,32

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INTERNATIONAL SEARCH REPORT

Int ional Application No

PCT/JP 02/00626

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 13620 A (LUNDBECK & CO AS H ;PERREGAARD JENS KRISTIAN (DK)) 23 June 1994 (1994-06-23) abstract page 1, line 5 - line 9 page 2, line 16 - line 32 page 3, line 10 - line 14 page 3, line 31 -page 4, line 1 page 5, line 10 - line 19 page 28, line 37 -page 29, line 4 claims 9,10	1-5, 19, 21, 22
A	WO 92 20655 A (UPJOHN CO) 26 November 1992 (1992-11-26) page 2, line 1 - line 7 page 5, line 15 - line 34 page 16, line 18 - line 25	1, 17-19, 21, 22, 30, 31
P, X	GARCIA-NANYA M., APIQUIAN R., FRESAN A.: "Atypical antipsychotics: Review article 'Los antipsycoticos atipicos: Una revision!" SALUD MENTAL, vol. 24, no. 5, October 2001 (2001-10), pages 37-43, XP008005976 abstract page 38, column 2, paragraph 2 - paragraph 4 page 39, column 2, paragraph 4	1-15, 20-29, 32
P, X	KECK P E ET AL: "BIPOLAR DISORDER" MEDICAL CLINICS OF NORTH AMERICA, W. B. SAUNDERS COMPANY, PHILADELPHIA, US, vol. 3, no. 85, May 2001 (2001-05), pages 645-661, XP008005975 ISSN: 0025-7125 page 645, paragraph 1 page 655, paragraph 3 page 656, paragraph 1 - paragraph 2 page 658, paragraph 2 - paragraph 3	1, 2, 20-22, 32
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/00626

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 17 and 21 relate to therapeutic applications which actually are not well-defined. The use of the definitions "a disorder of the central nervous system associated with 5HT1A receptor subtype" and "(a) neurodegenerative disease(s)" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the diseases specifically mentioned in claims 2-5, 16, 18, 19, 21 (excluding neurodegenerative diseases in general), 22-24, 30 and 31 and in the description, p. 16, line 23 - p. 17, line 19, and to the claimed diseases which fail to respond to the antipsychotic drugs mentioned specifically in claims 6-15 and 25-29.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 02/00626

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